NL Neurology Letters

Review Article

https://doi.org/10.52547/nl.1.2.48

Antioxidant supplements and cognition in Multiple Sclerosis: a systematic review

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Abstract

Background: Cognitive dysfunction is a debilitating characteristic of multiple sclerosis (MS) that affects approximately 60% of patients. To date, the only effective treatments for cognitive decline are cognitive rehabilitation and exercise training. While previous studies reported the beneficial effect of antioxidants on MS patients, several other studies investigated the effect of antioxidant supplements on the cognitive performance of MS patients. We aimed to conduct a systematic review to examine whether there is an association between antioxidants supplements and cognitive performance in MS patients.

Methods: We searched PubMed, Embase, Scopus, and Web of Science for the identification of relevant studies in November 2021. We included control trials, cohort, case-control, and cross-sectional studies which showed the effect of any type of antioxidants on cognitive performance in MS patients.

Results: After screening 12 papers were included in our study. Our review included three studies that examined the effect of ginkgo Biloba on cognitive performance, two examined the Mediterranean diet, and remained studies each investigated the vitamin A, Omega 5, Omega 3, estriol, epigallocatechin-3-gallate (EGCG), Boswellia papyrifera, and paleolithic diet. Overall, it seems that there were no benefits for antioxidant administration on cognitive performance in MS patients.

Conclusion: It is complicated to draw a conclusion regarding the effect of an antioxidant-containing regimen and cognitive performance in MS patients. Findings from included studies failed to unequivocally support the beneficial effect of antioxidant consumption on cognitive performance in MS patients.

Keywords: Antioxidants, cognition, Ginkgo Biloba, vitamins, diet

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Published online 30 December 2022

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Cite this article as: Nabizadeh, F., Sodeifian, F., Ghaderi, A., Sharafi, A. M., Balabandian, M. Antioxidant supplements and cognition in Multiple Sclerosis: a systematic review. Neurology Letters, 2022; 1(2): 48-60. doi: 10.52547/nl.1.2.48.

Introduction

Multiple sclerosis (MS) is an immune-mediated, and neurodegenerative disease of the central nervous system (CNS), characterized by demyelination, inflammation, and blood-brain barrier breakdown (1, 2). Inflammation of the CNS due to the immune cell infiltration and their cytokines are suggested as the probable cause of damage at the initial stages (3). Several environmental factors such as smoking (4), lack vitamins (5), and exposure to viral agents like Epstein Barr virus (EBV) (3) are associated with MS. Clinical manifestations of MS are ranged from sensory and motor disturbances including walking difficulties and fatigue to more cognitive and emotional impairments (3).

Cognitive impairment can occur at the early stages of MS with an estimated prevalence of about 45% to 65% (6, 7). There are considerable variations in the clinical course of cognitive decline among MS patients. Previous investigations revealed that learning and memory deficits are more common while visuospatial processing problems take place less frequently in patients suffering from MS (8, 9). As mentioned before MS patients usually experience degrees of cognitive decline along with physical impairment. Also, cognitive impairment is believed to be a sign of progression of disease (9). The etiology

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of the cognitive deficits in MS patients is still unclear, however several pathways like inflammation, neurodegeneration, and neural loss specifically in the brain cortex and thalamus play crucial roles in the development of cognitive impairment in these patients. In contrast, some patients with severe brain lesions showed no significant cognitive impairment (10). Although disease-modifying therapies can reduce relapse rates in patients, they are not much effective in improving or at least slowing down the progression of cognitive decline in MS patients. To date, the only effective treatments of cognitive decline are cognitive rehabilitation and exercise training (11). Several studies reported the association between oxidative stress and cognitive impairment in neurodegenerative diseases as well as MS (12). It is hypothesized that dietary antioxidants could improve cognitive performance and delay the onset of diseases such as AD (13). In contradiction, a recent investigation suggested that dietary anti-oxidants specifically vitamin E did not effectively improve cognitive performance in patients with dementia although, it decreased functional decline significantly (14). According to another study compounds such as epigallocatechin-3-gallate and α-lipoic acid showed significant anti-inflammatory effects in animal models of MS but, there were no benefits for vitamin E and Ginkgo biloba (15). Cutuli et al. investigated the impact of Omega-3 fatty acid, another substance with antioxidant effect, on cognitive function in mice and revealed the protective role of Omega-3 against cognitive decline and brain atrophy (16). Another study mentioned the fact that a diet providing a wide range of antioxidants, not a single antioxidant supplement is needed to observe significant improvement in symptoms of MS patients (17). Beydoun et al. demonstrated that dietary vitamin E is correlated with the improvement in multiple domains of cognitive performance such as verbal memory, verbal fluency, and psychomotor speed. These results were not only because of antioxidant effects of vitamin E, but also because of inhibiting the brain protein kinase C activity (13). While previous studies reported the beneficial effect of antioxidants on MS patients, several other studies investigated the effect of antioxidant supplements on the cognitive performance of MS patients (17). We aimed to conduct a systematic review to examine whether there is an association between antioxidants supplements and cognitive performance in MS patients.

Methods and Materials

This study was performed based on the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) (18).

Search strategy

We searched PubMed, Embase, Scopus, and Web of Science for the identification of relevant studies in November 2021. The following terms were used as our search strategy: (Antioxidant or hydroxyl radicals or peroxynitrite or peroxynitrite or superoxide or metal chelators or iron chelators or dietary intervention or diet plan or dietary supplements or anti-inflammatory or poly-unsaturated fatty acids (PUFAs) or selenium or blueberries or green tea or Ginkgo biloba extracts or coenzyme Q10 or turmeric or curcumin or vitamin C or vitamin E or vitamin A or phenolic or polyphenol or flavonoid or carotenoid) and (multiple sclerosis) and (Cognitive or cognition or cognitive decline or cognitive dysfunction or memory decline or dementia).

Eligibility criteria

We included control trials, cohort, case-control, and cross-sectional studies which showed the effect of any type of antioxidants on cognitive performance in MS patients. Case reports, animal studies, conference abstracts, letters, and book chapters were excluded.

Study selection

Two investigators (A.GH, A.SH) reviewed the title and abstracts to identify relevant studies. Then the same investigators screened the full-text of remaining studies for the final selection of eligible papers. Any disagreements were resolved by consulting with a third investigator (F.N).

Data extraction

The same reviewers (A.GH, A.SH) extracted the following information from included studies: Author, year of publication, region, study design, follow-up duration, sample size, EDSS score, type of antioxidant, dosage and frequency, number of placebo users, number of antioxidant users, mean age, cognitive tests, main findings and outcomes, other treatments. The extracted data were checked by the third investigator (F.N) to ensure accuracy.

Quality assessments

Publication bias of entered studies was performed using the Cochrane Risk of Bias Tool (19). The following domains were assessed: Bias arising from the randomization process, bias due to deviation from intended interventions, bias due to missing outcome data, bias in the measurement of outcomes, bias in the selection of the reported results.

Data synthesis and analysis

The extracted data were qualitatively compared and quantitative data represent as a percentage, mean, and range.

Results

Study selection

Our initial search yielded 1217 papers. Moreover, one additional study was retrieved manually. A total of 1014 papers were entered into our screening process after duplicate removal. After title and abstract evaluation, 208 studies were selected to enter the next step of screening. The remained papers were evaluated for their eligibility via full-text review, and finally, 12 papers were included in our study.

Characteristics of included studies and quality assessments

We identified eight randomized clinical trials (RCT) (20-27), two cohorts (28, 29), and two open trials (30, 31) studies with a total of 3136 subjects. Among included studies six were conducted in the USA, three in Iran, and one in each from Australia, Germany, and Israel. The age of entered subjects was ranged between 30 to 60 years. The risk of bias was acceptable in six studies (20-22, 25-27). However, in two studies (28, 29), the risk was high and in the remaining four studies (23, 24, 30, 31) there were some concerns.

Main findings

Our review included three studies that examined the effect of ginkgo Biloba (20, 27, 30) on cognitive performance, two examined Mediterranean dietary (24, 26), and remained studies one each investigated the vitamin A (28), Omega 5 (21), Omega 3 (29), estriol (22), epigallocatechin-3-gallate (EGCG) (23), Boswellia papyrifera (25), and paleolithic diet (31).

A study by Lovera et al, revealed that Ginkgo biloba use does not have any significant effect on most cognitive domains except the ability to inhibit cognitive interference which was measured by Stroop Color and Word Test (27). Another later study by the same author and same dosage and frequency did not find any significant difference in cognitive performance between the placebo group and Ginkgo biloba users (20). Moreover, a third study on the effect of Ginkgo biloba on cognitive function found an improvement of 14.10 points in the Wechsler memory scale (30). However, the limitation of this study was the lack of a placebo group to compare the results.

Razeghi-Jahromi et al. investigated the effect of the Mediterranean diet on cognitive performance and they found no improvement in cognitive function (26). Their proposed dietary program included healthy oils especially olive and olive oil, whole grains, vegetables, fruits, raw and unroasted nuts, and seeds, legumes, fish and seafood, poultry, eggs, low fat or skimmed dairy, and healthy plant-based foods. Red meat and fried foods were limited. Moreover, another study on the Mediterranean diet demonstrated that there was no meaningful improvement in cognitive function related to Mediterranean dietary in MS patients (24).

A study by Ruschil et al. investigated the therapeutic effect of vitamin A in four cases on cognitive status (28). There was no significant improvement in cognitive performance after 30 and 120 days of follow-up in these cases. On the other hand, omega 5 seems to be effective on verbal learning and memory deficits after three months (21). A large study by Jelinek et al. focused on the effect of omega 3 on quality of life in MS patients (29). In their investigation, four questions related to memory and cognitive deficits were asked from patients and demonstrated that MS patients who use omega 3 may have a better memory and cognitive status. However, they did not use a standard scale for cognitive measurements and the results should be interpreted carefully. MS patients receiving estriol had better information processing compared to placebos based on findings of Voskuhl et al. study (22). This investigation showed that after 12 months, Paced Auditory Serial Addition Test (PASAT) scores were significantly greater in the estriol group. Another study on Polyphenon revealed that EGCG intake does not improve cognitive performance in MS patients (23). Boswellia papyrifera, a medical herb, seems to be effective on improvement in visuospatial memory among MS patients (25). However, there was no significant improvement in other cognitive measures related to Boswellia papyrifera. Lee et al. study revealed that a paleolithic diet which typically includes lean meats, fish, fruits, vegetables, nuts, and seeds has a therapeutic effect on cognitive performance such as learning, memory, verbal and visual reasoning after three- and 12-months follow-up (31).

Discussion

Cognitive dysfunction is a debilitating characteristic of MS that affects approximately 60% of patients (32). The most common cognitive domains impaired in MS patients are learning, memory, attention, and processing speech impairment. Cognitive impairment accompanied by anxiety and depression leads to decreased quality of life in MS patients (33). To date, there is no approved treatment to reduce cognitive impairment in these patients to improve their quality of life. Therefore, non-pharmacological and complementary approaches could help these patients to counteract the cognitive damage.

Regarding the role of oxidative stress (OS) in the development of neurodegeneration and cognitive function in MS, it has been reported that infiltrated leucocytes to the brain produce great amounts of reactive oxygen species (ROS). Higher amounts of ROS have been shown to cause tight-junction alteration, loss of blood-brain barrier integrity, and rearrangement of the cytoskeleton (34). Furthermore, excess levels of ROS in the brain initiates myelin phagocytosis, damage to oligodendroglia and axons, which in turn leads to the progression of neurodegeneration and cognitive dysfunction in MS patients (34). ROS could damage proteins, nucleic acids, and lipids, leading to the mitochondrial release of cytochrome c, a major pathway involved in the neuronal apoptosis through the Bcl-2 family of proteins (35).

In this systematic review, we investigated the effect of antioxidant-containing regimens on cognitive domains of patients with MS. We found three studies reporting the effect of Ginko Biloba on cognitive performance in MS patients. The first study designed as RCT in 2012 by Levora et al. (20), did not find any significant effect of Ginko Biloba on any cognitive domains (Victoria Version of Stroop Color and Word Test (Stroop), California Verbal Learning Test II (CVLT-II), Controlled Oral Word Association Test (COWAT) and PASAT. Another study by the same investigator also reported no significant effect of Ginko Biloba on cognitive performance measured by CVLT-II, COWAT, Stroop Test, Symbol Digit Modalities Test (SDMT), and Adapted Version of the Useful Field of View Test (UFOV). However, according to the treatment effect trend, limited to the Stroop test, Ginko Biloba may improve mental flexibility, and susceptibility to interference but not working, verbal, and learning memory (20). The third study conducted by Noroozian et al. revealed that Ginko Biloba administration could significantly improve the WMS-subscale of memory test (Wechsler) and Multiple Sclerosis Impact Scale (MSIS29) (30). A controversial finding between these studies was the correlation between treatment response and severity of impaired memory. In contrast to the Levora study, Noroozian et al. demonstrated that less severity of impaired cognition was associated with a high treatment response. Briefly, among three studies reporting the effect of Ginko Biloba on cognitive performance, only one study supported the effective role of Ginko Biloba on cognitive

improvement among MS patients (30). However, this study lacked a controlled group, and further RCT and observational studies with the controlled group are required.

Mediterranean diet has recently attracted interest based on observational studies, suggesting that it could improve cognitive impairment and improve survival in affected individuals. Mediterranean diet is a plant-based diet that is high in unprocessed plant food including fruits, vegetables, grains, legumes, nuts, seeds, and extra virgin olive with a high amount of antioxidant complements. Furthermore, this diet consists of moderate fish, shellfish, and red wine and is low in animal food such as fish, eggs, and dairy (36). Two studies evaluated the effect of the Mediterranean diet on the cognitive function of patients. The first study conducted by Razeghi Jahromi et al. (26), was unsuccessful to show the effectiveness of the Mediterranean diet on cognitive performance in MS patients after follow-up. Supportively, the second study conducted by Sand et al. (37), revealed no statistically significant effect on cognitive function in MS patients. To better explain the role of this diet on cognitive function in MS, it should be considered that cognitive dysfunction in MS could occur during the first year of disease onset. While the mean duration of disease among patients was 8 years in the first study. Therefore, this intervention may be effective if administered at the appropriate time.

Regarding the effect of vitamin A on the cognitive function of MS patients, it has been demonstrated that all-trans retinoic acid (ATRA) shifts Th1/Th17 balance to Th2/Treg T lymphocytes, leading to clinical improvement of disease (38). However, in a study conducted by Ruschil et al. (28), no significant effect was observed in patients administered with ATRA. We should be cautious in interpreting the results of this study, as the sample size of this cohort study was very small (8 patients) and heterogeneous, meaning that each patient experienced a different duration of disease onset and most patients had failed previously approved therapies. Briefly, the results of this study are not enough to evaluate the effect of vitamin A on the cognitive performance of MS patients. More studies with larger and non-heterogeneous sample sizes are required.

Boswellia papyrifera is an Iranian traditional herb from the trees of the genus Boswellia (25). Anti-inflammatory and anti-arthritis effects of Boswellia extract have been supported by clinical studies (39-41). Moreover, it has been shown that Boswellia could improve the formation of new neuronal networks as in neurodegenerative diseases such as MS these networks are destructed which leads to cognitive impairment (42). We identified only one study that reported the effect of Boswellia papyrifera on cognitive domains (25). This study showed that this antioxidant could improve visuospatial memory, but not information processing speed and verbal memory. No significant effect of Boswellia on verbal memory could be due to its dose-dependent effect as was shown in two studies conducted by Mahmoudi et al.(43) and Farshchi et al (44). Therefore, to identify the exact effect of Boswellia on cognitive domains of MS patients, studies with different Boswellia papyrifera dosages are required. Moreover, the effect of Boswellia papyrifera on the cognitive performance of MS subjects could be influenced by sex as men in this study did not improve in the SDMT test.

Studies have shown that omega-3 has immunomodulatory and anti-inflammatory properties, making it clinically beneficial to reduce inflammation and improve cognition in MS patients. Moreover, it has been reported that omega-3 could increase the activity of glutathione peroxidase (GH), one of the most important endogenous antioxidants, leading to reduced inflammation and cytokine release (45). A study conducted by Jelinek et al. reported that omega-3 supplementation reduces perceived cognitive impairment in MS patients (29).

It is recommended to use an antioxidant-containing regimen diet accompanied by the administration of a healthy diet and lifestyle in these patients. This was well shown in Lee et al. investigation. In this study patients with MS were prescribed the home-base intervention consisting of 1) a modified Paleolithic diet; 2) exercise; 3) neuromuscular electrical stimulation; 4) stress management. According to the results of this study, the combination of a healthy lifestyle and diet could improve mood and cognition in MS patients (31).

To report the limitations of this study, we did not include case reports and non-English studies. Each study measured cognitive domains using different cognition scales with different sensitivity to track cognitive function in MS patients. Furthermore, some of the included studies did not use an antioxidant as monotherapy but rather used a multimodal such as a Mediterranean diet that is consisted of other neuroprotective factors and non-pharmacological interventions. Therefore, we cannot conclude that cognition improvement was solely dependent on the antioxidant itself.

It is complicated to draw a conclusion regarding the effect of antioxidant containing regimen and cognitive performance in MS patients. Findings from included studies failed to unequivocally support the beneficial effect of antioxidant consumption on cognitive performance in MS patients. This could be due to limited available studies on each nutrient, short duration of follow-up in some studies, and small sample size. In addition, subjects of several studies were heterogeneous, meaning that there were patients with different duration of disease onset. Furthermore, the sensitivity of each cognition test is different and may require a longer duration to detect cognitive performance in MS patients.

Deceleration

Funding

We do not have any financial support for this study.

Conflict of interest

The author declares no conflict of interest regarding the publication of this paper.

Ethical approval

Not applicable

Availability of data and material

The datasets analyzed during the current study are available upon request with no restriction.

Consent for publication

This manuscript has been approved for publication by all authors.

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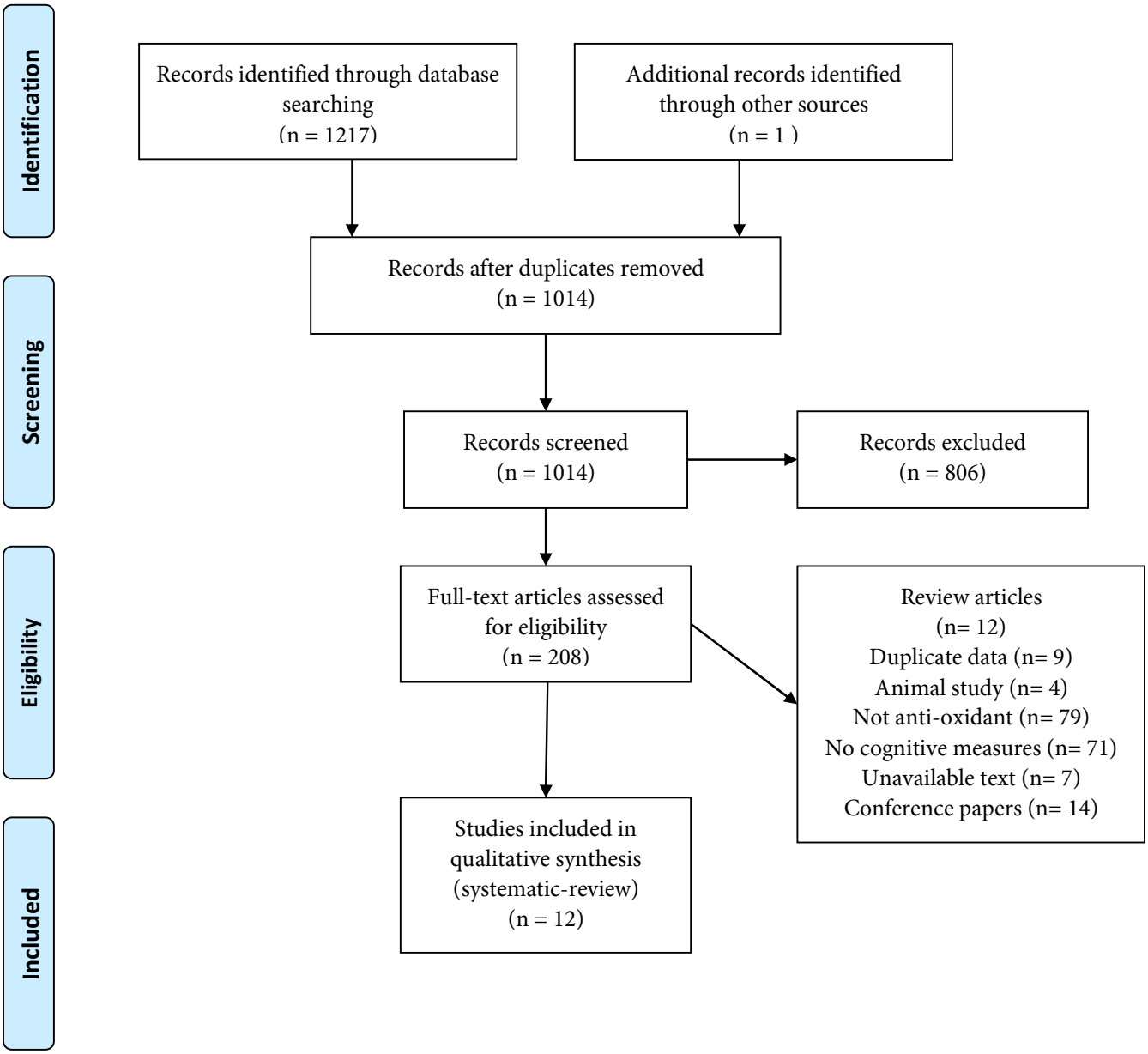

Figure 1. PRISMA flow diagram depicting the flow of information through the different phases of a systematic review

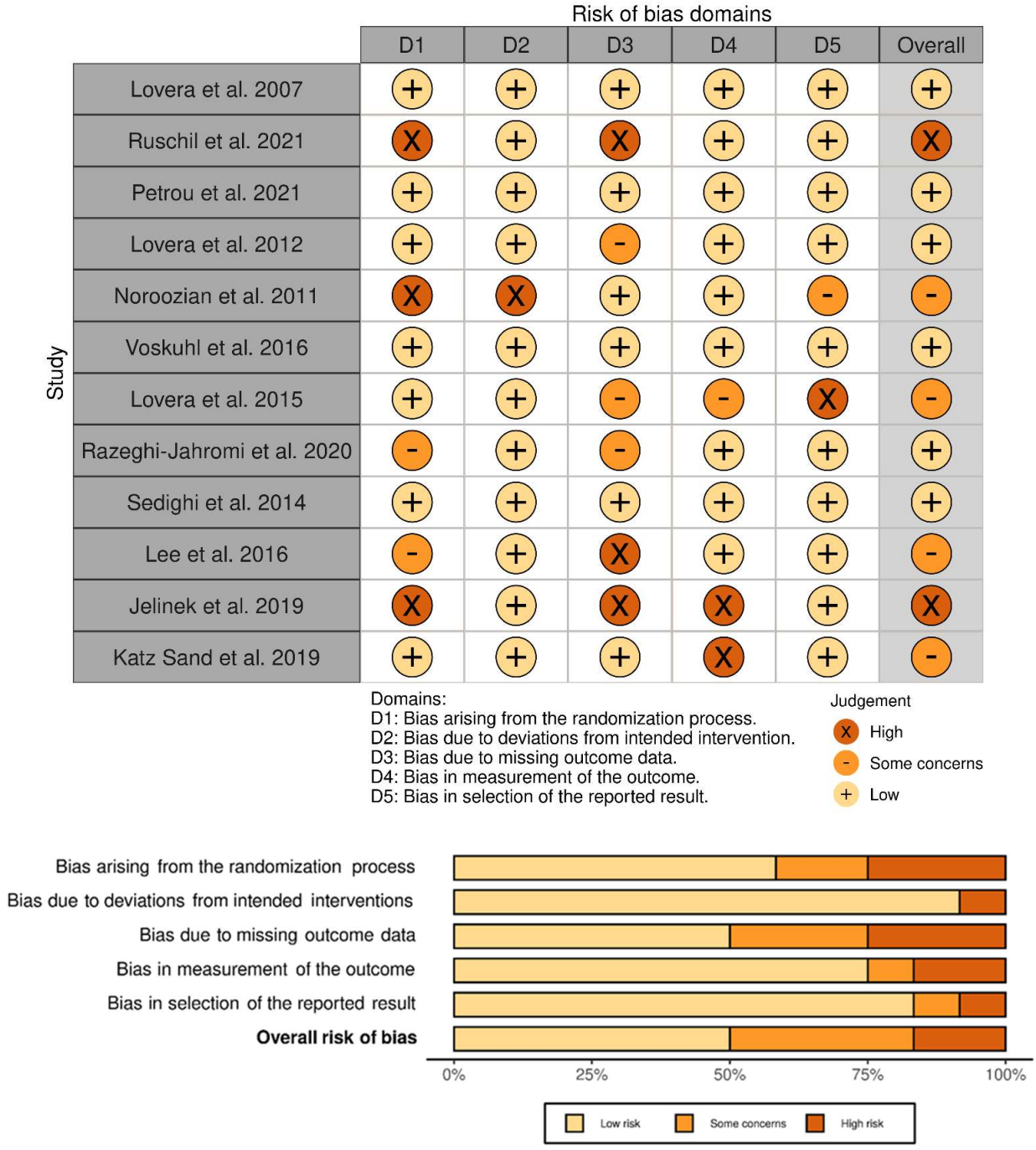

Figure 2. Assessment of risk of bias. (a) Graph of the risk of bias for the included studies, (b) graph of the risk of bias summary for the included studies.

Table1. Characteristics of included studies

Author	Year	Region	Study design	Follow-up duration	Sample size	EDSS score(placebo,AO)	Type of anti-oxidant	Number of placebos	Number of anti-oxidant users	Mean age (SD), (placebo,AO)
Lovera et al.	2007	USA	Randomized, double-blind, placebo-controlled trial	17 weeks (12 weeks of treatment)	39	Ranged 3.5-3.8	Ginkgo biloba	19	20	50.2(8.0), 47.8(6.7)
Ruschil et al.	2021	Germany	4 cases+control cohort	NR	4+50		Vitamin A			
					patient 0(index)	6.5				56
					patient 1	5				59
					patient 2	5.5				60
					patient 3	4				39
					control cohort	4.92±0.23				53.9 (3.1)
Petrou et al.	2021	Israel	Randomized double blind clinical trial	NR	22	Anti-oxidant:4.5±1.9, Placebo:5±1.2	GranaGard (Granalix Bio Technologies LTD)	10	12	Anti-oxidant:47.7±14.0, Placebo:50.1±8.9
Lovera et al.	2012	USA	Randomized placebo-controlled trial	NR	120	4±2,4±2	Ginkgo biloba	59	61	53 (9.5),51.3 (8.6)
Noroozian et al.	2011	Iran	Open trial	8 weeks	30	NR	Ginkgo biloba	0	30	33.7±8.5
Voskuhl et al.	2016	USA	Randomised, double-blind, placebo-controlled trial	24 months	164	2.1±1.1,2.2±1.2	Estriol	81	83	37.1 (7.3), 37.7 (7.6)
Lovera et al.	2015	USA	Randomised placebo-controlled trial	6 months	10	Median (Range): 4 (1–6.5)	Polyphenon E: Epigallocatechin-gallate (EGCG)	0	10	Median (Range):45 (39–56)
Razeghi-Jahromi et al.	2020	Iran	Single-blind randomized controlled trial	1 year	72 (34 intervention, 38 control): 56 cases were analyzed for cognitive effects (27 intervention, 29 control)	2.40±1.07, 2.27±1.14	Mediterranean diet, except for wine and some other unspecified foods which were eliminated according to the Iranian culture based on religious beliefs	29 cases were analyzed for cognitive effects	27 cases were analyzed for cognitive effects	34 (9), 34 (8)
Sedighi et al.	2014	Iran	Randomized, double-blinded, and placebo-controlled study	2 months	80(76 finished the study)	NR	Boswellia papyrifera	40 (38 finished)	40 (38 finished)	36.95 (8.90), 36.21 (8.25)
Lee et al.	2016	USA	One-arm, open-label feasibility trial	12 months	19	6.2±1.0	Paleolithic diet	0	19	51 (6.5)
Jelinek et al.	2019	Australia	cohort	4 weeks	2490	NR	Omega 3	1730	760	45.5 years of the whole cohort
Katz Sand et al.	2019	USA	Randomized-controlled trial	6 months	36	2 (0–5), 2 (0–3)	Modified Mediterranean dietary program	18	18	41 (30–49), 44 (37–51)

NR: Not Reported, EDSS: Expanded Disability Status Scale

Table2. Interventions and clinical findings

Author	Year	Type of anti-oxidant	Dosage and frequency	Number of placebo	Number of anti-oxidant users	Cognitive domain	Main findings and outcomes	Other therapies
Lovera et al.	2007	Ginkgo biloba	120 mg twice a day	19	20	CVLT-II PASAT COWAT SDMT UFOV Stroop Color and Word Test	no differences no differences no differences no differences no differences The Ginkgo biloba group was 4.5 seconds faster:The difference in the adjusted means for the color-word interference condition of the Stroop test showed a statistical trend favoring the Ginkgo biloba group (4.5 seconds) which did not reach statistical significance after Bonferonni's adjustment for multiple comparisons. There was a statistically significant interaction between the baseline performance on the color-word interference condition of Stroop test and treatment suggesting that subjects who were more impaired on the Stroop at baseline experienced the most improvement with Ginkgo biloba treatment.	NR
Ruschil et al.	2021	ATRA(all-trans retinoic acid)	a 30-day induction phase with daily oral administration of ATRA(all-trans retinoic acid) (45 mg/m2) was followed by 3 cycles of consolidation (daily medication during the first 15 days of a 30-day cycle) and multiple cycles of sustainment (3-month cycles with treatment during the first 15 days, planned for 6 cycles or until sustained disease progression)			MSFC, PASAT		
			6 cycles of sustainment		1	no cognitive domain	MS symptoms continuously improved	Induction therapy with Idarubicin (12 mg/m2 on day 2, 4, 6, 8) and cytarabin (A 100 mg/m2 /24h on day 1), Three cycles of consolidation (anthracycline-based cytarabine), 6 cycles of maintenance therapy (6-mercaptopurine daily, methotre weekly)
			4 cycles of sustainment		1	PASAT	minimal, not statistically significant or clinically relevant improvement at day 30 and day 120 that were not sustained at day 210 and day 300:no significant changes were observed	symptomatic therapies (e. g. anti-spastic)
			2 cycles of sustainment(300 days)		1	PASAT	severe cognitive and motor worsening after the first cycle of sustainment therapy (day 210)	symptomatic therapies (e. g. anti-spastic) + additional immunomodulatory dr (intravenous corticosteroids)
			2 cycles of sustainment(300 days)		1	PASAT	minimal, not statistically significant or clinically relevant improvement at day 30 and day 120 that were not sustained at day 210 and day 300:no significant changes were observed	symptomatic therapies (e. g. anti-spastic)
				30		no cognitive domain	annual worsening of EDSS	35 were untreated, the other received various treatments (rituximab n = 4, ocreli n = 2, repeated high-dose i.v. methylprednisolon n = 4, dimethyl fumarate n = interferone-beta n = 2; natalizumab n = 2)
Petrou et al.	2021	Omega 5	Group anti-oxidant were given omega 5 for the first three months, and placebo for the next three months and controls received placebo for the first three months, and omega 5 for the following three months. All patients received omega 5 for additional six months	10	12	CVLT-II	Beneficial effect: The z score for CVLT-II, significantly increased (from a mean of 0.891 to 1.415, median: 0.799 vs 1.199, p = 0.012, Wilcoxon signed rank test) at 3-months in the group of patients who were treated with omega 5, as compared to baseline. Using linear MMRM model (Mixed-effect model for repeated measures) applied for analyzing the difference between the two treatments and adjusted for the carry-over effect analysis, the effect of treatment with Omega 5 on CVLT-II remained statistically significant at p = 0.05./The overall average z-score of all three cognitive functions was significantly improved in the three months of omega 5 treatment (-0.0077 at 3 months vs 0.462 at baseline, p = 0.034, Wilcoxon rank test). During the same 3-months period there were no significant changes in the placebo-treated group. For the patients receiving GranaGard in the initial 3 months, the value of z score of CVLT-II remained high (z = 1.415) also at the following three months (while they received placebo), suggesting a longer lasting effect for at least 3 months after discontinuation of the drug	The designated chronic immunomodulatory MS treatment
						BVMT-R	A similar trend to CVLT-II (but not statistically significant either using the Wilcoxon signed rank test or the MMRM) was seen during the first 3 months treatment-period	
						SDMT	no change	
Lovera et al.	2012	Ginkgo biloba	120 mg twice a day	59	61	Stroop Color-Word Tes-Victoria	no differences	No disease-modifying therapy,glatiramer acetate,Interferon B-1a 30 ug once week,Natalizumab,Mitoxantrone,Azathioprine,Mycophenolate,Interferon B-1a(once a week,44 ug 3 times a week,B-1b 0.25 mg every other day,30 ug once a w changed to GA,44 ug and methotrexate,44 ug and GA)
						CVLT-II	no differences	

						CVLT-II COWAT PASAT PDQ MSNSQ	no differences no differences no differences no differences no differences	
Noroozian et al.	2011	Ginkgo biloba	240 mg/day, TDS except one that received 120 mg/day, TDS	0	30	Wechsler test (Wechsler memory scale)	An improvement of 14.10 points were observed (p<0.001). All participants except one had improvement. no significant correlation between the results of post treatment Wechsler and MSIS-29 tests. No significant difference between men and women (p=0.35). no significant difference between age groups (p=0.07 and p=0.16). no significant difference (p = 0.12) comparing RRMS and SPMS participants. Type of MS drug had no effect on improvement of memory impairment (p=0.73). The mean value of memory improvement was 17.30 points in participants with high mental activity and this was more than that of participants with low mental activity (12.50 points). This difference was, however, not statistically significant (p=0.10). The mean value for improvement of memory impairment was 18.60 points in university educated participants (who had more than 12 years of education) and 12.40 points in non university educated participants (who had less than 12 years of education); this was also statistically significant (p=0.05). Linear regression analysis showed that less impairment at baseline indicated by lower score on the Wechsler test is associated with a greater treatment effect (p=0.028, B=0.346)	Twenty five participants used Interferon Avonex (7), Rebif (5) and Betafron participants used Novantrone and 3 participants used no drug as the treatme MS
Voskuhl et al.	2016	Estriol	8 mg daily	81	83	PASAT	no differences at 24 months; however, at 12 months, PASAT scores were significantly greater in the estriol group than in the placebo group, and in a post-hoc analysis of patients with a score of less than the median of 55 at baseline, improvements at 12 months were 4·7 points in patients who received estriol and 1·6 in patients who received placebo, whereas there was no significant effect in patients with higher scores at baseline. Because estriol concentrations were low at 24 months, which is when PASAT scores were no longer significantly improved in the estriol group compared with the placebo group, we assessed correlations between estriol concentration and PASAT score. Estriol concentration was directly correlated with PASAT score. similar benefits of estriol treatment	Glatiramer acetate(20 mg/day),progestin (norethindrone 0·7 mg) and seconc matched to progestin
Lovera et al.	2015	Polyphenon E:Epigallocatechin-gallate (EGCG)	Two capsules twice daily (200 mg of EGCG per capsule; total daily dose 800mg)	0	10	Spatial Recall cognitive testing Cognitive measures	No significant changes	No disease-modifying therapy,glatiramer acetate
Razeghi-Jahromi et al.	2020	Mediterranean diet, except for wine and some other unspecified foods which were eliminated according to the Iranian culture based on religious beliefs	5 meals each day (consisting of more healthy oils especially olive and olive oil, whole grains, vegetables, fruits and raw and unroasted nuts and seeds, legumes, and healthy plant based foods. Fish and seafood for about 2 times per week, poultry, eggs, and low fat or skimmed dairy (daily to weekly) was recommended. limitation of red meat, fried foods, and refined grains in addition to minimizing consumption of simple sugar, sugary foods and beverages, processed meat, and animal based fats to as low amounts as possible.	29 cases were analyzed for cognitive effects	27 cases were analyzed for cognitive effects	MACFIMS	Intergroup P value (between placebo and intervention), intergroup P value(intervention)	NR
						PASAT SDMT California Verbal Learning Test-2nd edition (CVLT-II) total learning CVLT-II BVMT-R COWAT JLO D-KEFS D-KEFS total sorting score	0.87/0.25 0.19/0.41 0.95/0.5 0.11/0.12 **0.02**/0.51(meaningful difference) 0.75/0.86 0.33/0.21 0.51/<0.001 0.14/<0.001	

Sedighi et al.	2014	Boswellia papyrifera	Capsule 300 mg, twice a day)	40 (38 finished)	40 (38 finished)	BICAMS	Inter group P value Note:sex might be influential. All patients whose SDMT improved were female in contrary to males. The male patients did not improve in that test (P = 0.024).	NR
						SDMT	P = 0.2000	
						CVLT-II	P = 0.1700	
						BVMT-R	P < 0.001(meaningful difference)	
Lee et al.	2016	Paleolithic diet	leafy green vegetables, sulfur-rich vegetables, and/or deeply colored fruits and vegetables, Omega-3 oils, plant protein, animal protein, Nutritional yeast, Kelp, Algae, nondairy milks	0	19	Cognitive(CSI/T, D-KEFS, WAIS)	P values for changes from: 1)Baseline to 3 months-2) 3 to 12 months-3) Baseline to 12 months	the diet was accompanied by these modalities: (2) an exercise program (stret strengthening of the trunk and lower limb muscles); (3) neuromuscular el stimulation (EStim) of trunk and lower limb muscles; and (4) stress management (meditation an massage).
						CSI/T	Learning/Memory: 0.13-0.17-0.02	Baseline to 12 months P value related to vegetable/fruits consumption=0.006- to 12 months P value related to gluten/diary/eggs deletion=0.001
						CSI/T	Speed: 0.35-0.34-0.67	Baseline to 12 months P value related to vegetable/fruits consumption=0.74- to 12 months P value related to gluten/diary/eggs deletion=0.63
						CSI/T	Attention: 0.42-0.21-0.05	Baseline to 12 months P value related to vegetable/fruits consumption=0.04- to 12 months P value related to gluten/diary/eggs deletion=0.21
						D-KEFS	Language:0.14-0.02-0.003	Baseline to 12 months P value related to vegetable/fruits consumption=0.005- to 12 months P value related to gluten/diary/eggs deletion=0.001
						D-KEFS	Switch(Complex Verbal Fluency): 0.87-0.05-0.02	Baseline to 12 months P value related to vegetable/fruits consumption=0.01- to 12 months P value related to gluten/diary/eggs deletion=0.06
						WAIS	Similarities (Verbal Reasoning): 0.01-0.04-0.0001	Baseline to 12 months P value related to vegetable/fruits consumption<0.(Baseline to 12 months P value related to gluten/diary/eggs deletion=0.(
						WAIS	Matrix (Visual Reasoning): 0.28-0.002-0.002	Baseline to 12 months P value related to vegetable/fruits consumption=0.003- to 12 months P value related to gluten/diary/eggs deletion=0.001
Jelinek et al.	2019	Omega 3	Omega 3 supplement: fish oil incl. high potency or Flaxseed oil or Both fish/flaxseed	1730	760	Note: A subscale within the Multiple Sclerosis Quality of Life (MSQOL-54) was used. 4 questions were related to cognition. Respondents indicated how much of the time in the prior four weeks they had experienced each symptom, 1 representing all of the time and 6 representing none of the time.	4 questions: 1. Have you had difficulty concentrating and thinking? 2. Did you have trouble keeping attention on an activity for long? 3. Have you had trouble with your memory? 4. Have others, such as family members or friends, noticed that you have trouble with your memory or problems with your concentration?	NR
						(at least two questions all the time, most of the time, good bit of the time) and omega 3 intake	p=0.008	
						(at least three questions all the time, most of the time, good bit of the time)) and omega 3 intake	p=0.022	
						(at least two questions all the time, most of the time, good bit of the time) and DHQ total score	p<0.001	
						(at least three questions all the time, most of the time, good bit of	p<0.001	

							(at least three questions all the time, most of the time, good bit of the time) and DHQ total score	p<0.001	
Katz Sand et al.	2019	Modified Mediterranean dietary program	Encouraged the intake of fresh vegetables and fruits, fish, nuts, legumes, whole grains, avocados, and use of olive oil in cooking. It advised against the intake of meat (including red meat as well as poultry), dairy, "white" grains, and processed foods. Participants were also advised to limit salt intake to 2 g/day and to abstain from eating for at least 12 h per night (recommended 7 p.m. to 7 a.m.)	18	18	MACFIMS	no statistically significant difference	NR	

NR: Not Reported, EDSS: Expanded Disability Status Scale, SDMT: Symbol Digit Modalities Test, CVLT-II: California Verbal Learning Test-II, PASAT: Paced Auditory Serial Addition Test, COWAT: Controlled Oral Word Association Test, UFOV: Useful Field of View Test, BVMT-R: Brief Visuospatial Memory Test, PDQ: Perceived Deficits Questionnaire, MSNSQ: Multiple Sclerosis Neuropsychological Screening Questionnaire, MACFIMS: Minimal Assessment of Cognitive Function in MS, JLO: Judgment of Line Orientation Test, BICAMS: Brief International Cognitive Assessment for MS, WAIS: Wechsler Adult Intelligence Scale, D-KEFS: Delis-Kaplan Executive Function System, CSI/T: Cognitive Stability Index test